Medical Progress

Functional Aspects of the Rejection Of Transplanted Kidneys

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SINCE RENAL TRANSPLANTATION involves acts of trauma such as ischemia, denervation and ureteric mobilization and division, any assessment of the effects of transplantation per se requires information about the effects produced by each factor individually. Without this information, the clinician may be perplexed about the functional patterns presented by kidneys after transplantation. Indeed, Ogden et al (1965) stated, with little justification, "Little information is available concerning functional capacity of renal transplants." Without a great deal of information concerning the autotransplanted kidney, one is without control data and this has led to several unjustified conclusions about the behavior and morphology of allotransplants.

Control data concerning the effects of transplantation are widely scattered in the literature. Table 1 lists, in a fairly logical sequence, some details required for any reasonable assessment of the effects of transplantation. Each experiment was aimed at assessing the effect of a single factor on subsequent renal function. So far as my own experience goes, the discovery of the impaired function of a kidney autotransplanted to the carotido-jugular circulation of a dog initiated the whole investigation (Dempster 1950). It will be observed that after several procedures involving some kind of damage to the kidney a low concentrated urine in large amounts is evoked. Post-transplant diuresis was exactly the problem which Ogden et al (1965) observed in their human cases and which initiated their own careful and critical assessment of immediate functional pattern after transplantation. It will also be seen that in some circumstances the immediate functional pattern involving a low concentrated urine continues permanently while in others normal function recovers after a few weeks.

Any control study, it will surely be conceded, must involve observations on the autotransplant. From Table 1 it is clear that up to half an hour of total ischemia causes only slight, transient functional changes and that within a few hours normal function is restored. Cutting the renal artery and vein and resuturing is followed by loss of concentration for two to six days and presumably a varying period of total ischemia accounted for these results in ten dogs. Cutting the renal artery alone and resuturing in three dogs was followed by recovery of concentration in 48 hours. Transplanting a kidney with its intact adrenal gland does not influence the early functional impairment after transplantation (Dempster 1955 b), yet a normal kidney deprived of its adrenal will continue to lose salt relative to the contralateral kidney (Dempster and Graber 1953). Sectioning and full mobilization of the ureter appears to be the key to impaired function after transplantation. The natural history of the sectioned ureter (Dempster and Daniel 1956) indicated that a mild hydroureter and hydronephrosis develop soon after sectioning and these are sufficient to impair concentrating ability for as long as the abnormality lasts.

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TABLE 1.—*Assessment of the Individual Factors Involved in Early Impaired Function After Kidney Transplantation*

Experiment Performed	*Immediate Function (0 hours to 2 weeks)*	*Late Function (after 4-6 weeks)*	*Comment*
Autotransplant kidney to neck (dog) with skin ureterostomy Dempster and Joekes (1953)	Diuresis: Hyposthenuria Salt losing GFR falls Blood flow normal	No change. Responds to anti-diuretic drugs and emotional states	Ureterostomy on skin leads to hydronephrosis at first mild and later moderate
½ hour ischemia by clamping renal artery of normal kidney Dempster (1956-57)	Normal concentration within 4 hours	Normal concentration	Transient excess protein in urine for 4 hours
Section of artery and vein followed by suture. Ureter left intact. (Dempster, unpublished)	Normal concentration in 48 hours in some cases but in others up to 6 days is required.	Normal concentration	Indicates that denervation and ½ hour ischemia are not important
Unilateral adrenal-ectomy and homo-lateral renal function Dempster and Graber (1953)	Diuresis: Subnormal concentration. Excess loss of NaCl relative to contralateral kidney	No change	No change in GFR or ERPF
Autotransplant kidney to pelvis with ureter re-implanted in bladder Dempster, Joekes and Oeconomos (1955)	Diuresis: Hyposthenuria Salt losing Blood flow, ERPF } normal in 4 hours	Normal function	Mild hydronephrosis subsides after a few weeks
Autotransplant left kidney, adrenal and ovary to pelvis. Ureter re-implanted in bladder. Dempster (1955b)	Diuresis: Hypothenuria Salt losing Blood flow, ERPF } normal in 4 hours	Normal function	Presence of the adrenal has no effect on the impaired function
Autotransplant cooled preserved (6-20 hours) kidney to pelvis Dempster, Kountz and Jovanovic (1964) Aboul-Enein et al (1965)	Anuric or oliguric	Slow gradual return to normal function	Recovery similar to acute tubular necrosis
Allotransplant kidney to pelvis. Ureter re-implanted in bladder (Dempster 1970)	Diuresis: Hyposthenuria Salt losing Blood flow, ERPF } normal in 4 hours	Under adequate immuno-suppression normal or near normal function	Sudden decline in function starting with acute reduction in ERPF indicating rejection

The Nature of Post-Transplant Diuresis

In assessing post-transplant diuresis Ogden et al (1965) concluded that the pattern of function resembled that following the removal of obstructive uropathy in which a loss of sodium occurs. Salt loss is also associated with acute ischemic tubular damage and this factor, also, has to be taken into account in assessing the immediate post-transplant diuresis. Dempster et al (1955) concluded that the cause of this functional pattern lay in the sectioned, denervated ureter and that edema of its wall, mild hydroureter and hydronephrosis together with some neuromuscular incoordination produced the immediate functional pattern of the autotransplant rather than an osmotic diuresis due to excess urea in which sodium loss is not characteristic (Clapp and Robinson 1969). Ogden et al (1965) found no rela-

tionship between the blood urea nitrogen (BUN) level before the transplant and the magnitude of the diuresis. The presence of urea in the proximal tubule tends to decrease sodium reabsorption so that in the uremic subject an excess serum urea contributes, to some extent, to an osmotic diuresis in the post-transplant kidney and a complicated situation occurs in which the excess sodium excretion tends to be a consequence of the urea osmotic diuresis (Maher et al 1963; Mudge et al 1949).

The Functional Pattern of the Allotransplanted Kidney

If an allotransplanted kidney is now substituted for an autotransplanted kidney, the same immediate functional pattern can be observed. If the allotransplant is from a live donor a functional pattern similar to that observed for the autotransplant is seen but since the recipient is uremic the diuresis is excessive because of the excess urea, salt and water and the expansion of circulating blood volume in such patients. An expanded extracellular fluid volume is not a major factor, as the glomerular filtration rate (GFR) is frequently grossly subnormal for some weeks after transplantation. The subnormal GFR in the immediate post-transplant period requires explanation. The diuresis in such circumstances can reach 20 liters in 24 hours. It was this kind of observation which Ogden et al (1965) were concerned about since massive diuresis is clinically alarming. An osmotic diuresis due to excess electrolytes and urea will lead to dehydration unless corrected. Because a disturbance has occurred in concentrating ability, polyuria will continue when hydration is maintained. With the polyuria there will be a loss of sodium which will require correcting.

When the excess urea, salt and water have been eliminated the diuresis declines and the daily urine volume and concentration approach normal values unless acute rejection occurs which will cause a decline in all measurements of renal function. The effective renal plasma flow is profoundly disturbed first and this leads to the subsequent changes in tubular function. Once a functional pattern approaching normal is attained, any decline in function must be regarded as an indication of rejection unless proved otherwise.

The ideal conditions involved in transplanting kidneys directly from live donors seldom occur in current practice. The function of cadaveric kidneys immediately after transplantation varies a great deal from adequate function to poor function and from oliguria to anuria lasting for several days or weeks. The total ischemia time may be greatly increased, cooling in the course of preservation at 4°C increases the renal peripheral resistance so that imperfect perfusion is not immediately achieved, and in addition there may have been a low renal blood flow for several hours before the death of the donor. All these factors create a new clinical situation after the new blood flow has been established, and one must await whatever functional pattern evolves. After a pattern approaching normal has evolved or stability at a level below normal has been reached, any decline from this base line must be regarded as indicating rejection unless proved otherwise.

The immediate functional characteristics of a successful renal pelvic autotransplant in a normal animal are as follows:

- Prompt excretion of hypotonic or isotonic urine in large quantities. The diuresis is probably due to impaired sodium reabsorption from the proximal tubule and this is probably linked to the mild and usually transient hydronephrosis following sectioning of the ureter.
- Reduction in the renal blood flow and effective renal plasma flow for one to four hours.
- Reduced GFR for several weeks. The GFR is usually the last feature to return to normal.
- Transient excess loss of sodium.
- Excess proteinuria lasting for some hours (Dempster 1954). The protein is derived from tubular, ureteric mucosal damage and to some extent glomerular damage. The selectivity of this urinary protein, therefore, will be poor. Electronmicroscopy demonstrates cell debris in the lumena of the tubules (Figure 1).
- Arteriograms indicate normal distribution of blood even though the total blood flow is reduced during the first few hours (Dempster 1954).

Low GFR in the Immediate Post-Transplant Phase

Immediately following transplantation, there is a short period (one to four hours) of low GFR due to a hemodynamic upset which involves inadequate perfusion of the outer renal cortex (Dempster 1971a). Adequate function continues

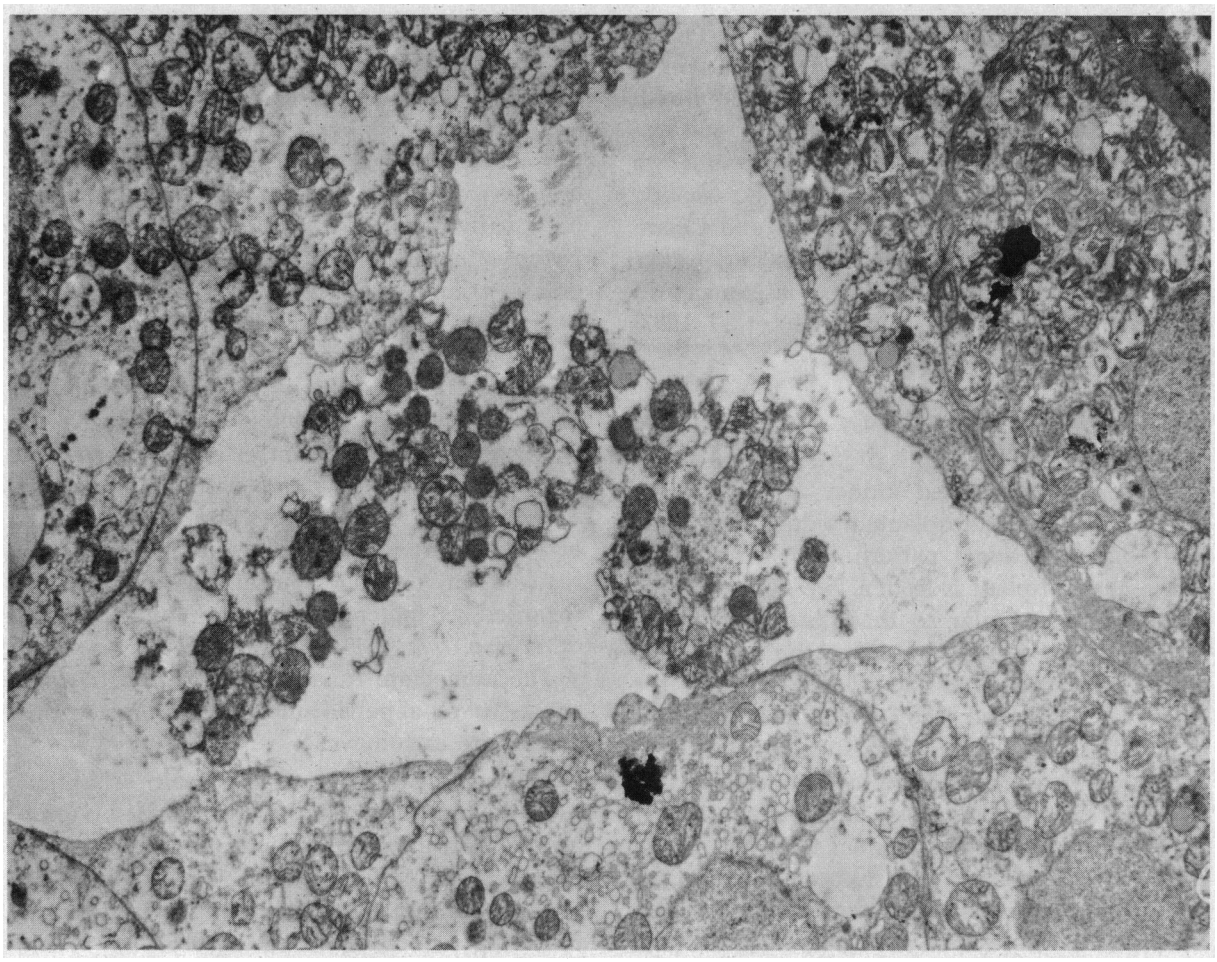

Figure 1.—An electronphotomicrograph of an autotransplanted kidney four hours after transplantation. This section demonstrates the extrusion of cytoplasmic organelles—mitochondria, lysosomes, etc., into the lumen of the tubule. This is a non-specific effect of sudden total anoxia. Reduced from x 9,750.

although there is some impairment of quality. The total renal blood flow (RBF) and the effective renal plasma flow (ERPF) usually recover to normal values within four hours but the GFR although it rises from a low immediate post-operative level remains subnormal for weeks or months. The cause of this prolonged reduction in GFR should be sought amongst those factors normally controlling GFR—glomerular permeability, capillary blood pressure, intracapsular hydrostatic pressure and colloid osmotic pressure. Of these, the only obvious disturbance following transplantation is in the intracapsular hydrostatic pressure. Complete ureteric obstruction will increase this hydrostatic pressure so that the GFR is reduced. Following full mobilization and section of a ureter in the course of transplantation, some ureteric incoordination and surgical trauma rather than clear obstructive nephropathy produce a mild hydroureter and hydronephrosis (Paccione et al 1965) which usually subside with the passage of time and allow the GFR to rise. If the ureter does not recover, the kidney will not recover (Dempster et al 1955).

Definitive assessment of renal function can be made only some weeks after transplantation. The functional characteristics then are—barring any rejection episodes and complications—as follows:

A return to normal concentrating ability.

A GFR which improves with time, indicating that hypertrophy is occurring or the ureteric disturbances are becoming resolved or both.

A return of normal total renal blood flow and effective renal plasma flow.

Reversal, in some cases, of diurnal rhythm.

The immediate functional characteristics of a kidney derived from a live donor and allotransplanted to a patient in gross renal failure will

depend partly on technique and partly, and usually more importantly, on the chemical state and hydration of the patient. Under optimum conditions an allotransplant will behave essentially as the autotransplant does but, in addition, the environment in which a kidney finds itself will cause adjustments so that salt and water balance will be achieved. Thus an osmotic diuresis is superimposed on the already transiently impaired reabsorptive capacity of the proximal tubule. The functional characteristics of an allotransplanted kidney at a later stage will depend on the adequacy of immuno-suppression and the presence or absence of complications. It is obvious from the data (Figure 6, Dempster 1955a) that allotransplanted kidneys vary in their ability to tolerate the changes induced by the rejection process. At four days, for example, it will be seen that some kidneys become anuric while others do not (Dempster 1955a).

The Cooled Cadaveric Kidney Allotransplant

The behavior of the cooled, preserved cadaveric kidney can be controlled, to some extent, by observing the behavior of the cooled preserved autotransplanted kidney. After a period of oliguria or anuria a recovery phase similar to the functional pattern of recovering acute tubular necrosis has been well observed.

An assessment of the function of a cadaveric cooled and preserved allotransplant to a patient in renal failure must be divided into various stages:

1. *Immediate post-transplant phase*

   There may be no function for several hours, days or weeks—depending on the period of warm ischemia before cooling. During this time only a renogram can provide any information about the total renal blood flow. An arteriogram (Figure 2) will indicate inadequate perfusion of the outer cortex, and particularly spasm of the glomerular capillaries and a poor nephrogram will indicate a failure of filtration in the outer glomeruli.

2. *Onset of function*

   The onset of function resembles that following acute renal failure when the diuretic phase occurs. Gradually all aspects of renal function improve and may reach normal levels but this is contingent on reperfusion of the outer cortex. Any sudden decline in function after this stage must be regarded as an indication of rejection unless proved otherwise. In practice, a variety of functional states evolve and these are determined by—

   a) Age of the donated kidney.
   b) Initial degree of damage before and during preservation.
   c) Any pre-existing disease in the donor kidney—pyelonephritis for example.
   d) Technique.
   e) The adequacy of immuno-suppression as reflected in the number and severity of acute rejection episodes and the ease with which they were suppressed.
   f) The degree of tolerance to immuno-suppression.
   g) The presence of urological complications – for example, urinary fistula or blockage.
   h) The nature of the renal disease of the recipient.

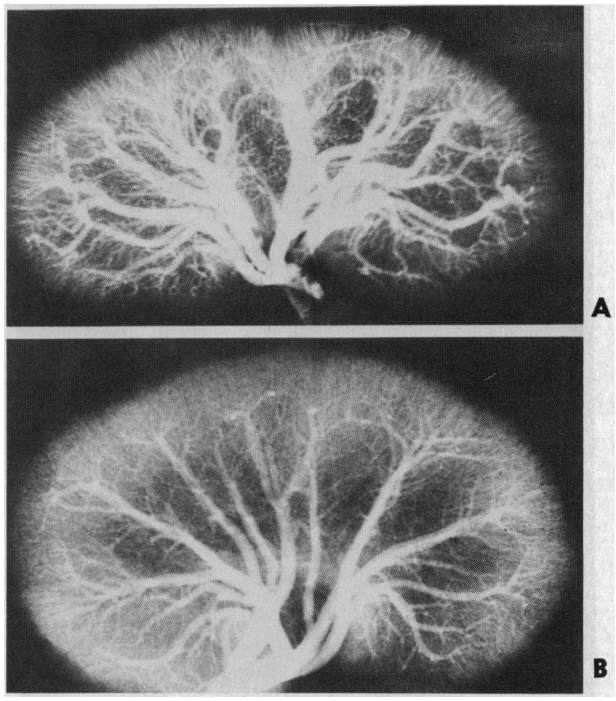

Figure 2.—Arteriogram taken 30 minutes after transplantation following preservation by cooling for 20 hours at 4°C. The perfusion of the outer cortex is poor in spite of using vasodilators. (b) A normal arteriogram of a functioning kidney 60 minutes after transplantation. The general effect of well filled glomeruli in the cortex creates a snowstorm effect as distinct from the "pallisade" effect of interlobulars whose afferent arterioles and glomeruli are not being normally perfused as demonstrated in 2A.

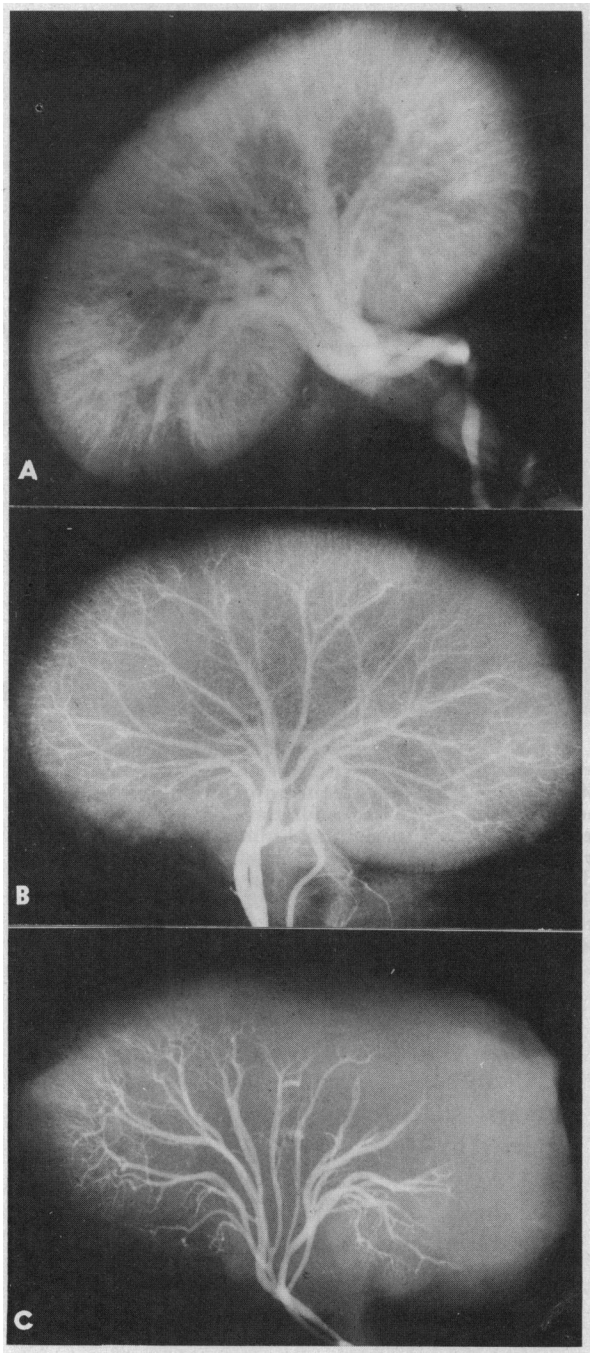

Figure 3.—Arteriograms of first-set allotransplanted kidneys (canine)—at various stages of rejection. (Normal, Figure 2 b). (a) Indicates early impairment in the outer cortical flow associated with profound fall in effective plasma flow and oliguria. (b) Indicates gross changes in the outer cortical flow together with total afferent vasoconstriction associated with anuria. (c) Indicates a very late phase associated with complete anuria and very low total renal blood flow.

In any long-term assessment of renal function it is frequently impossible to correlate morphology and function. An apparently good clinical state frequently belies quite extensive parenchymal and vascular damage (Figure 3 a). The functional pattern of slow decline is that which any chronic damage to vessels and glomeruli will produce. At a certain level of damage, however, there will be a decline in overall function which will become slowly progressive. At this stage one has to consider removing the severely damaged transplanted kidney, returning the patient to the dialysis program and arranging for another transplant to be performed. The problems involved are discussed later.

Rejection—Differential Diagnosis

Rejection, acute or chronic, is the onset of renal failure due to a series of changes in the vasculature of the allotransplanted kidney leading to inadequate perfusion. The onset of acute renal allotransplant failure is the result of acute changes not only in the capillaries and venules but also in the vessels of all calibers. The onset of chronic renal allotransplant failure is the result of slow and gradual changes in the vessels, interstitial fibrosis and glomerular damage. The morphological aspects of rejection are primarily confined to the vessels, and the tubules are involved secondarily; acute tubular necrosis is associated with acute rejection and tubular atrophy is associated with chronic obliterative changes in the vessels. Similarly in the allotransplanted heart the myocardial changes are secondary to changes in the coronary vessels at all levels (Dempster 1969a). There are some limitations to descriptions such as "acute" and "chronic" in relation to rejection. The "chronic" can sometimes occur rather acutely and early and the "acute" can be sometimes superimposed on the "chronic." Basic to all these rejection processes is increased vascular permeability (Dempster 1970).

A complete description of acute rejection requires data derived from several sources—clinical, physiological, biochemical, morphological and immunological (Table 2). Correlating these data can be quite difficult. Minimal morphological changes may occasion severe and alarming clinical signs and symptoms, and sometimes gross morphological changes are associated with

TABLE 2.—*Aspects of Acute Rejection*

Discipline	*Features*			
	TOXIC HYPERTENSIVE SYNDROME			
Clinical	Oliguria or Anuria	Large tense painful kidney : Fever, Malaise, Anorexia : Blood cultures negative.	Increased urinary sediment : Hypertension :	Urine sterile :
Physiological	Afferent vascular spasm : Non-pulsatile flow : Acute stretching of arteries :	Decreased solute excretion :	Rapid decline in ERPF and GFR :	Relatively slow fall in total blood flow.
Biochemical	Absolute fall in kidney enzyme levels :	Increased excretion of enzymes in urine :	Progressive upset of pyruvate metabolism :	
	Protein of poor selectivity			
Morphological	Vascular damage with increased vascular permeability :	Fluid loss into interstitium : mural oedema of vessels :	Cell invasion : plasma cell—endothelial cell confrontation :	Acute tubular : necrosis :
Immunological	Cell-mediated : (small lymphocyte)	Humoral antibodies (anti-HL-A) Evidence for both processes is tenuous.		
	The dilemma of first and second—set rejection			

an apparently adequate clinical state. Morphology and function are frequently not well correlated especially where chronic changes are concerned. Since any given morphological change is associated with a certain functional pattern it is obvious that a clinical diagnosis of rejection can be quite difficult. Acute and chronic rejection are consequences of acute and chronic failure of perfusion. Thus, failure of renal perfusion from whatever cause will produce a characteristic functional pattern. The onset of renal failure due to rejection has to be carefully differentiated from other causes of renal failure and other causes of a similar set of symptoms. The physiological changes recorded in rejecting allotransplants are as follows: a reduced GFR, ERPF, RBF, urine volume and solute excretion (particularly sodium); a renogram which either shows a reduced uptake or an accumulation curve. A differential diagnosis, therefore, must consider the following: renal artery stenosis, increased pressure on the renal vein and ureteric obstruction. Arteriography will certainly differentiate rejection from the other possibilities.

Acute rejection of allotransplanted kidneys can be referred to as the hypertensive-toxic syndrome (Dempster 1970). This syndrome involves oliguria or anuria, fever, anorexia and malaise; and added to these, hypertension is common (Dempster 1953b)—symptoms which are rather similar to those of pyelonephritis but the urine of the rejecting kidney is usually sterile and blood culture of the recipient is negative.

The only feature of the toxic-hypertensive syndrome which we can surely account for is the onset of oliguria or anuria caused by afferent renal vasoconstriction (Figure 3). Fever is difficult to account for and is not due to infection (Dempster 1953b); anorexia and malaise are not due to an incipient uremic state since these features are present in dogs retaining one normal kidney and the hypertensive state is not just due to renal ischemia (Dempster 1970). A similar toxic state with anorexia occurs in recipients of heart transplants when rejection is in its early phase (Dempster 1969b).

Inadequate Renal Perfusion as the Cause of Functional Failure

What is the evidence that inadequate perfusion is responsible for functional failure? The factors leading to impaired renal perfusion are indicated in Chart 1. Gaps in our knowledge relate to the cause of the initial inflammatory response leading to increased capillary and venular permeability (Dempster 1970).

Increases of renal vein pressure, insufficient to induce significant change in clearance of PAH and creatinine, result in a large percentage decrease in sodium excretion and urine volume. A decrease in perfusion pressure will reduce solute excretion proportionately with the reduction of

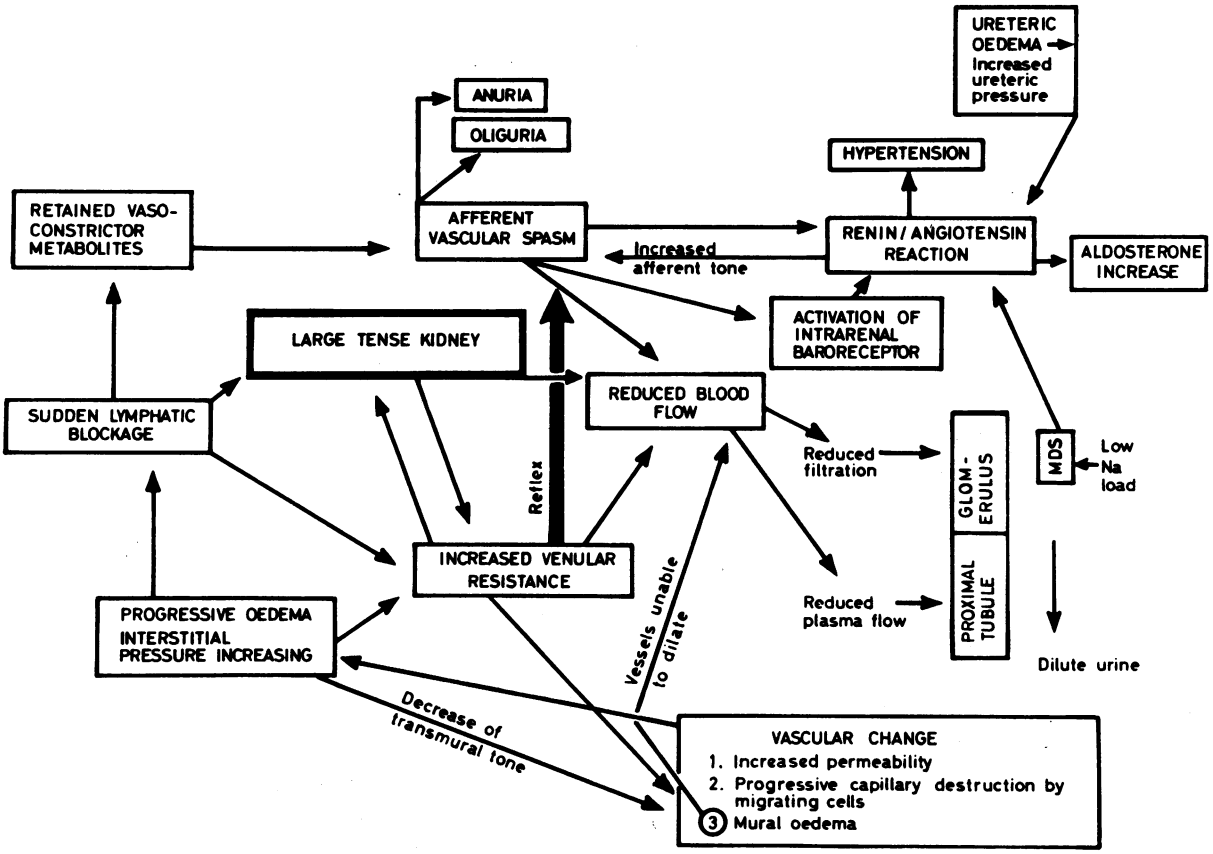

Chart 1.—The scheme demonstrates the effects of increased vascular permeability on renal hemodynamics of the first-set allotransplanted kidney. (Dempster W J, 1970: Brit J Exp Path 51:149, 1970).

GFR after a certain stage of arterial constriction. With minimal decrease in arterial pressure, reductions in excretion of Na and the urine volume occur before any changes in renal blood flow and GFR are detected.

Alterations in perfusing pressure or renal vein pressure are rapidly progressive in a kidney about to undergo acute rejection. Thus, there is seldom time enough to detect a sharp fall in sodium excretion before any detectable decline has occurred in GFR and ERPF. Usually, by the time a routine assessment is made all factors have declined. It is perhaps an unattainable ideal to expect to detect a single change in functional pattern which is well in advance of other parameters of function.

If kidneys are examined during the phase of acute rejection it will be observed that the hilar fat surrounding the renal vein is extremely edematous (Dempster 1970—Figure 5). Pressure by this edematous area surrounding the renal vein may be the first cause of the fall in solute excretion. The next phase involves an increase in venular pressure due to a rising interstitial pressure. At a certain critical stage afferent vasoconstriction is produced and the perfusion pressure in the outer cortex falls. This will lead to reduced solute excretion, reduced urine volume and a precipitate fall in ERPF. Should any other hemodynamic upset be required a raised ureteric pressure due to edema and compression at the site of anastomosis can be added to the above factors.

These conclusions are derived from experiments lasting a relatively short time. Rejection is a process involving a progressive decrease in renal profusion and a measure of this factor is central to any diagnosis of acute rejection. The 15-minute Phenol Red Test is cheap, easy, accurate and repeatable. In our early observations (Dempster 1953a) it was found that the total renal blood flow was very low at the stage of anuria. It took some time to realise that the onset of rejection coincided with oliguria and that anuria was a much later feature of rejection. If

the total renal blood flow is measured at oliguria it may be found that there is no statistical fall before the crisis of frank rejection (Dempster 1967). If the blood flow is measured at other intervals during the functioning phase no apparent gross decline in flow can be recorded. Also, for a few hours after transplantation total blood flow may be 50 percent of normal and yet there is usually an adequate urine flow because the distribution of blood is normal (Dempster 1954). The difference between this early low flow and the flow at the time of oliguria and anuria is one of distribution of total flow. Rejection is associated with not only a fall in total renal blood flow but also with a change in its distribution so that the outer cortex is deprived of perfusion. Vasoconstriction of the afferent system appears to be responsible, and once vasoconstriction occurs the total renal blood flow declines relatively slowly but the effective renal plasma flow falls profoundly and suddenly. Arteriography at this stage of rejection will reveal outer cortical ischemia and generalized afferent spasm (Dempster 1955a). There will now be an oliguric phase with delayed passage of contrast material through the kidney. By the time anuria is established the total renal blood flow will have fallen considerably. Later the values for total blood flow are virtually those that could correspond to medullary flow alone (Dempster 1953a; Jackson and Mannick 1964). Because total renal blood flow in such conditions can be reduced to 10 percent of normal and hence approximately the value for medullary flow, it would be misleading to conclude anything about the state of medullary flow. China ink injections reveal, in such vasoconstricted kidneys, that medullary flow is decidedly reduced whenever outer cortical flow is reduced (Dempster 1971a). What causes the vascular spasm?

Due to progressive leakage of fluid a stage is reached when the increased interstitial pressure causes increased venular resistance. This appears to precipitate afferent vascular spasm. This can be experimentally produced by constricting the renal vein of an allotransplanted kidney. If the renal vein constriction is released at the end of an hour a reversal of flow occurs and allows normal perfusion of the outer cortex (Dempster 1970). The exact cause of raised venular resistance and afferent vascular spasm has not yet been defined.

Non-Pulsatile Flow in the Renal Artery

Soon after the onset of afferent vascular spasm the flow along the extrarenal portion of the renal artery becomes non-pulsatile (Dempster 1955a; Henry et al 1969). Depulsation is known to depress tubular excretory function (Many et al 1967). The onset of non-pulsatile flow is not entirely connected with increased peripheral resistance because in early anuria of whatever cause, in second-set reactions or in immediately anuric cadaveric kidneys pulsatile flow along the renal artery as far as the arcuates continues for 24 hours or more. With reversal of rejection pulsatile flow in the renal artery returns simultaneously.

Sudden Anuria Due to Thrombosis or Rejection

Renograms taken during acute rejection are not very revealing since they cannot differentiate the various causes of any deformity of uptake or excretion phase. Renograms will not clearly demonstrate the distribution of blood which is all important. Thus, although a more traumatic procedure, arteriography, when well performed, can be a greater aid in diagnosing rejection. This procedure, however, is hardly necessary in a patient who is ill and in whom other features of rejection can be more easily measured. Serial osmolalities, for example, can be valuable in arriving at a differential diagnosis. If the osmolality has been near normal or has been stabilized at a certain level and the last value before anuria continues the previous trend, one can diagnose renal artery thrombosis. If, however, the final osmolality before anuria reveals a value much lower than the preceding values, a diagnosis of rejection is reasonable since the acute rejection process, in its early stages, involves inadequate renal perfusion and hence a pronounced decrease in solute excretion.

Late or Chronic Rejection

Metabolic studies of allotransplanted kidneys are limited by the linked nature of metabolic pathways to the fundamental pyruvate stage. Any disturbance here (Dempster and Kountz 1966) will have far-reaching effects. Recently O'Brien et al (1970) reported early disturbances of phospholipid metabolism and fatty acid oxidation which would fit earlier disturbances at the pyruvate stage although this may be difficult to

demonstrate. It should be realized that all kidneys rendered totally anoxic for a period up to 60 minutes at body temperature reveal physical damage to the tubule cells which is reversible. It it possible that the allotransplants, in a proportion of instances, cannot replace the lost organelles quickly enough.

Glomerular Changes

In the immediate post-transplant phase the GFR can be decidedly reduced without detectable signs of damage. We have previously ascribed this to ureteric incoordination which can result in some upset in glomerulo-tubular balance. However, the decreased GFR, per se, may not be the main factor in the glomerulo-tubular balance which is controlled by several factors—(1) tubular volume which influences the reabsorptive state, (2) the rate of removal of fluid from the peritubular interstitium into the capillary network which is sensitive to variations in colloid osmotic pressure and the hydrostatic pressure within the capillary, (3) the perfusion pressure, any small decrease of which can decrease sodium excretion without changing GFR, and (4) excess aldosterone secretion due to stress will inhibit sodium and so water excretion. Of these, the most important is perfusion pressure, which appears to be decreased due to increased renal peripheral vascular pressure (Dempster 1970).

In acute rejection soon after transplantation, the glomeruli are usually characteristically normal in histological sections. In rejection occurring some months after transplantation glomerular damage is very common although probably not the main cause of renal failure. The extent of the glomerular damage varies and may lead to the onset of the nephrotic syndrome, when doubly refractile lipid bodies are detected (Harlan et al 1967). Other investigators deny that transplant proteinuria ever evolves into nephrosis.

Live donor kidneys leak protein immediately after transplantation and this lasts several hours (Dempster 1954). This has been attributed to ischemic damage to the tubules and is of poor selectivity. From then on, proteinuria of poor selectivity will reappear during phases of acute rejection where conditions involving inadequate perfusion prevail. What causes the glomerular changes that appear some weeks or months after transplantation remains obscure. In some instances the glomerular changes represent a recurrence of a preexisting glomerulonephritis and in others it would seem that transplantation antigen-antibody complexes are responsible. Although subepithelial deposits and humps are commonly found in cases of membranous and post-streptococcal glomerulonephritis and subendothelial deposits and humps are found in some cases of kidney allotransplants, a differential diagnosis of subendothelial deposits involves a consideration of causes such as nephrotoxic serum, acute glomerulonephritis, lipid nephrosis, lupus nephritis, diabetic nephropathy, chronic glomerulonephritis, anaphylactic purpura, and nephrosclerosis.

Although glomerular changes can present, microscopically (McKenzie and Whittingham 1968),

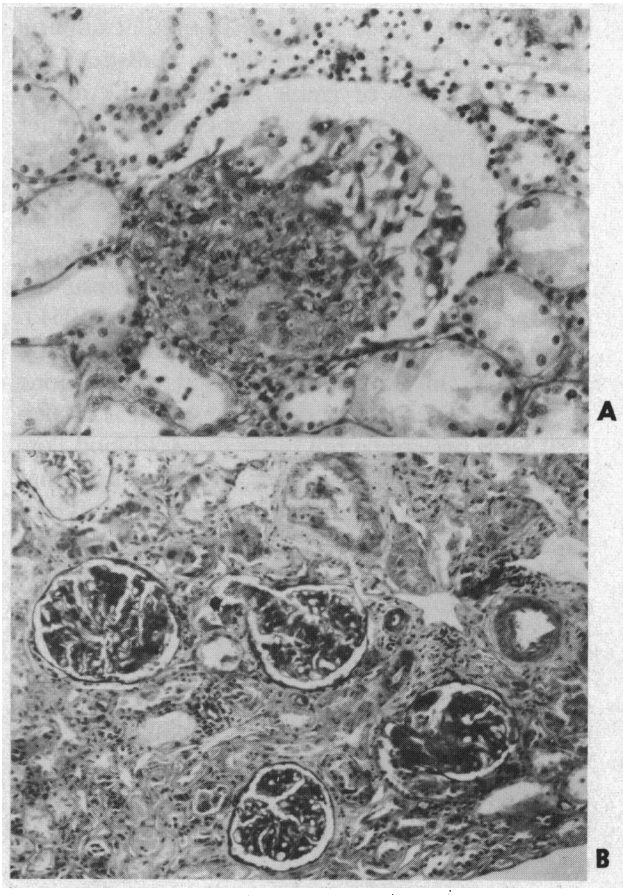

Figure 4.—Photomicrographs of glomerular lesions in human first-set allotransplanted kidneys associated with an adequate general clinical state. (a) A glomerular lesion closely resembling focal glomerulo-nephritis (Heptinstall & Joekes 1963). Picro-Mallory x 160. (b) Glomerular lesion involving large fibrinoid deposits in about 40 percent of glomeruli associated with a GFR reduction of 60 percent. Picro-Mallory x 160.

TABLE 3.—*Aspects of Late or Chronic Rejection*

Discipline	*Features*
	ACUTE SYMPTOMS IF ACUTE REJECTION IS SUPERIMPOSED
Clinical	Hypertension : Anemia : Progressive decline in well-being as progressive decline in renal function develops : Infections : Bone disturbances.
Physiological	Progressive decline in GFR, solute excretion, ERPF and total renal blood flow.
Biochemical	Progressive increase in urinary sediment—tubular casts, enzymes, cells of all types. Protein of poor selectivity
Morphological	Progressive vascular obliteration : Interstitial fibrosis : Edema : Glomerular damage Tubular atrophy : Cell invasion of variable proportions.
Immunological	Recurrent glomerulonephritis Antigen-antibody complex glomerulonephritis Cell-mediated or humoral antibodies (anti-HL-A) or a new unknown complex.

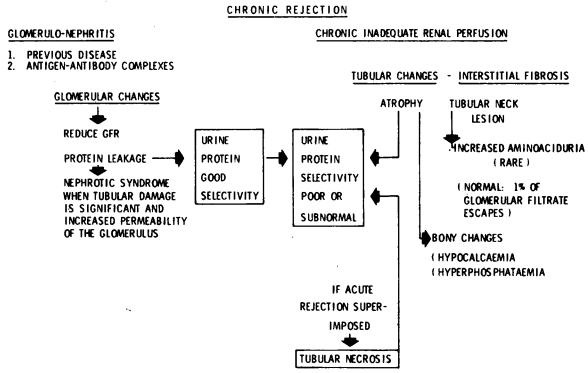

Chart 2—Chronic Rejection Process

an alarming appearance they are frequently accompanied by quite adequate renal function (Figure 4 b). A lesion resembling focal glomerulonephritis, as described by Heptinstall and Joekes (1963) can be observed in a human kidney following allotransplantation (Figure 4 a). It is rare, however, for allotransplanted kidneys to show glomerular changes without at the same time showing developing interstitial fibrosis and the obliterative vascular lesion. For this reason proteinuria will always be of poor selectivity so that this test is seldom of real value. It is the rate and extent of the obliterative vascular lesion which is going to dictate how long the kidney will continue to function adequately. In the long run, the vascular lesions will lead to gradual tubular atrophy and chronic renal failure (Table 3, Chart 2); and, indeed, one is frequently amazed at the extent of morphological damage commensurate with an adequate clinical state. The GFR, however, can be reduced by 66 percent without necessarily upsetting glomerulo-tubular balance.

Tubular Changes (Chart 2)

Ischemia probably causes the necrosis of cells in the neck of the proximal tubule (Figure 5) (Darmady et al 1956). Although this lesion resembles an acute form of the "swan neck" deformity observed in Fanconi syndrome, no evidence of increased aminoaciduria was found during acute rejection. In only one human case (Massry et al 1967) has increased aminoaciduria been described, and that under conditions which are difficult to assess. Several tubular functions were depressed, particularly an inability to excrete hydrogen ions which is characteristic of the "neck" autotransplanted kidney, but without excess aminoacid excretion.

Disturbance of Tubular Transport Calcium-Phosphate Relationships

Calcium-phosphate bone interrelationships become progressively disrupted in renal disease. After renal transplantation the various chemical abnormalities of uremia are quickly corrected but parathyroid involution does not always occur and may require surgical intervention. When GFR falls below 25 to 30 ml a minute, hyperphosphatemia occurs and this stimulates parathyroid hormone (PTH) release. Steroids tend to protect against the development of hyperphosphatemia but care must be taken to ensure against hypercalcemia. Abnormalities in vitamin D metabolism may be reversed after renal transplantation and absorption from the gut becomes more efficient and, in the absence of steroids, may predispose to the development of hypercalcemia and nephrocalcinosis.

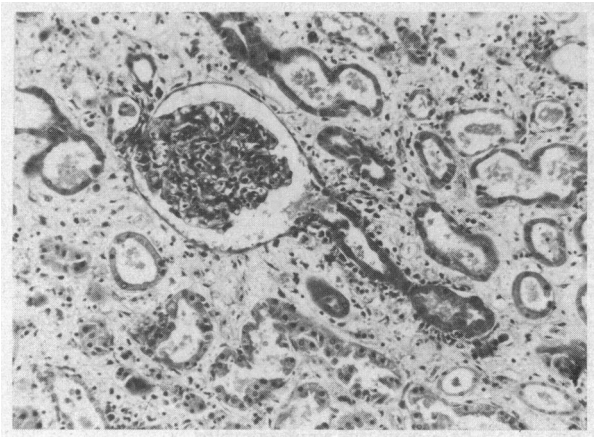

Figure 5.—Photomicrographs of a section of human allotransplanted kidneys rejected acutely. Debris in Bowman's space consists of fragments of neck tubule cells. Hematoxylin-eosin stain x 90.

Interstitial Changes—Fibrosis

The cause of interstitial fibrosis is probably long-standing interstitial edema. Collagen is frequently observed in the vicinity of plasma cells lying in the interstitium. There are perhaps two factors, then, leading to the laying down of collagen which eventually leads to tubular atrophy and death of tubules—focally. This will, in turn, lead to proteinuria of poor selectivity and hence is of some diagnostic value in that it indicates that tubular as well as glomerular damage has occurred.

Renal Vascular Changes

Renal vascular changes include increased permeability, intertubular capillary and venular disorganization by circulating plasma cells and an obliterative process involving vessels of all sizes but mainly the interlobular. Terms such as acute and chronic vascular lesions do not accurately reflect the tempo of the latter two disease processes in the immuno-suppressed human. These processes frequently are associated together in the rejection episodes soon after transplantation. The obliterative lesion can be very acute and capillary disorganization can be superimposed on the more chronic obliterative lesion and evoke, clinically, an acute rejection episode. Chart 1 indicates the pathophysiological result of a combination of renal vascular changes in an allotransplanted kidney. Once vascular permeability is increased and is not kept under control, hemodynamic changes will occur which lead to afferent renal vascular spasm. Sudden failure to perfuse adequately the outer cortex can account for the renal failure of an acute rejection episode. Vascular function may only be impaired to the extent that the larger vessels are unable to dilate on demand due to the intramural edema. The ability to dilate on demand is the most important function of an artery. There is quite a range of arteriographic patterns, depending on the strength of the rejection process and the time when the arteriogram is made.

A reversal of rejection involves a reversal of the afferent arterial spasm, particularly the exclusion of the outer cortical circulation (Figure 3). The rationale for using large doses of hydrocortisone to reverse rejection is now clear, since this drug acts by stabilizing vascular permeability and so allows flow to return to the outer cortex with subsequent recovery of renal function. However, as a result of the temporary rejection episode certain sequelae follow which will be discussed later.

Division of Labor Among the Nephrons

Since the outer cortical glomeruli and nephrons are particularly involved when the cortical spasm occurs, some attention should be paid to the suggestion (Barger 1966) that the tubules supplied by the outer cortical glomeruli are adapted to salt excretion. A diagramatic representation of the cortical vessels has been presented by Barger which suggests that the classical view of the arrangement of the outer cortical vessels is not correct. The diagram suggests that special vessels arise from the arcuates and proceed to the outer cortex without giving off afferent arterioles until they reach the outer cortex—something in the manner of branches at the tops of coconut trees. Spasm of these vessels, it is suggested, will considerably reduce the excretion of water and salt. In a prolonged search, I have not been able to detect such vessels in neoprene casts of kidneys (Dempster 1971b). Nevertheless, there is some other evidence to support the interesting suggestion that tubules arising from the glomeruli of the outer cortex are concerned in salt excretion (Horster and Thurau 1968; Dempster 1971b).

Hypertension as a Sign of Rejection

As a sign of rejection, hypertension is fairly common. The cause is rather obscure and evidence for a renin/angiotensin involvement is lacking. Hypertension following transplantation,

of course, can be due to causes other than rejection—glomerulonephritis in the kidneys of the recipient, fluid and salt imbalance, excess steroids, stenosis of the renal artery due either to stricture or rejection disease.

Hypertension associated with rejection occurs in both acute and chronic rejection and it is rather doubtful if the same mechanism operates in both processes. There has been some difficulty in correlating blood pressure, plasma renin activity and aldosterone secretion during rejection episodes in allotransplanted kidneys. It was originally considered that hypertension during rejection was due to renin release in an ischemic kidney which was demonstrated by arteriography and renal blood flows (Dempster 1953b). Sometimes hypertension is not present during rejection, either in dog or man, and this is just as mysterious as when it is present, since ischemic or rather underperfused kidneys are common to both clinical conditions. Though the renin content of a kidney is reported to be reduced by denervation and steroids (as in kidney allotransplantation presumably) there appears (in a large proportion of rejection episodes) little interference with the mechanism which allows hypertensive states to be reached.

Plasma renin activity is probably raised because there is some impairment of perfusion of the outer cortex following the afferent spasm. However, this raised plasma renin activity may not be associated with a raised blood pressure. It has been argued (Dempster 1970) that since the renin/angiotensin system does not explain the hypertension of rejection it may be that rejection in some way inhibits a hypotension-promoting mechanism in the kidney.

Proteinuria as a Sign of Rejection

Protein excreted in quantities greater than 3.5 grams per 24 hours per 1.73 square meters of body surface occurs in both acute and chronic forms of rejection. This increased proteinuria is usually of poor selectivity because tubular damage and ureteric mucosal damage is involved. Very rarely does glomerular damage occur alone, and so a proteinuria of good selectivity rarely occurs. Excess proteinuria may proceed to frank nephrosis in some cases but some units report that they have not encountered this complication. Nephrosis has been diagnosed on the basis that lipoid bodies as well as protein appeared in the urine. Histuria (Antoine et al 1969) is well correlated with gross interstitial and tubular damage.

Microvascular Angiopathic Hemolytic Anemia (MAHA) as a Sign of Rejection

It is not clear from other disease processes involving MAHA what the cause is although fibrin strands have been suggested by some investigators (Bull et al 1968). Since during rejection the capillaries and venules of allotransplanted kidneys are often under attack and laminar flow is disturbed, it might seem that the scene is set for damage to red blood cells from this source alone. The red blood cell in dogs appears to be more fragile than in humans, and perhaps this may explain why MAHA is relatively rare in the human rejecting allotransplanted kidney (Lichtman et al 1968). When it does occur it is a very late sign and, indeed, it is debatable whether rejecting kidneys should be retained until so late a stage.

Oliguria or Anuria in the Immediate Post-Transplant Period

The recent interest in so-called hyperacute rejection has been bedeviled by too enthusiastic a use of immunological catch-phrases, like Shwartzman reaction and Arthus reaction, employed usually without any reference to the theoretically necessary prerequisite of a hypercoagulable state or fibrinolysis. Another factor contributing to confusion is that few clinics have studied this problem experimentally. In several respects dog and man are not similar from an immunological point of view. Nonetheless, reports of immediate post-transplant anuria in human second kidneys from different donors (Williams et al 1969) are sufficiently close, from a clinico-pathological point of view, to earlier observations of second-set canine kidneys (Dempster 1953a, 1969a) that at least a start can be made by formal experimentation on dogs, followed by an assessment of what is common to the human situation. My object now is to try to set out the conditions under which one may so classify any given immediate post-transplant anuria as a second-set rejection or, as it is loosely referred to, *hyperacute rejection* (Kissmeyer-Nielsen et al 1966).

The current evidence against a Shwartzman-type of reaction occurring in those so-called hy-

peracute rejection is as follows: (1) No evidence of previous hypercoagulability (Pineo et al 1970) and this agrees with some human evidence (Colman et al 1969). (2) The non-specificity of polymorph margination evoked by any severe hemodynamic upset (Dempster 1969a). This rules out the suggestion of Clark et al (1968) that polymorphs are effectors of rejection. (3) The failure of Arvin to influence a second-set rejection (Pineo et al 1970) indicates that intravascular coagulation plays a minor role in the second-set reaction. Detection of fibrin within a kidney is significant only in relation to the events preceding its deposition. In any severe renal hemodynamic upset, fibrin will be deposited but this does not reveal what has precipitated the hemodynamic crisis (Dempster 1969a). (4) The Shwartzman reaction is dependent on functional defects of the reticulo-endothelial system and the second-set reaction is not. (5) The Shwartzman reaction is abrogated by denervation but the second-set reaction is not. (6) The severity of the Shwartzman reaction is reduced by phenoxybenzamine but this has no effect on the second-set reaction. (7) Decomplementation has no effect on the second-set reaction (Dempster and Brown 1971) and this makes it highly improbable that HL-A antibodies, which are dependent on complement fixation—*in vitro*, at least—as the mediators of second-set rejection.

There are, of course, similarities between the generalized Shwartzman reaction and the second-set kidney transplant reaction viz:

1. There is glomerular dilatation with stasis in the early phase before fibrin deposition (Dempster 1953a; McKay and Rowe 1960).
2. Vasomotor disturbances lead to increased venular resistance and afferent vasoconstriction (Dempster 1953a; Schneider et al 1968; Pineo et al 1970).
3. In the late phase there is glomerular contraction and fibrin deposition (Dempster 1953a; Pineo et al 1970).

The Detection of Renal Deposited Fibrin and Fibrinuria as Tests of Rejection

Fibrin and fibrinogen are not normally detectable in urine. Antoine et al (1969) proposed the term *fibrinuria* to denote the presence of fibrinogen-like material in the urine from human transplanted kidneys. Although fibrinuria is a constant feature in the early post-transplant phase, it is due to several varied causes. Two main conclusions emerge from their work: (1) There is a close correlation between high steroid dosage and fibrinuria, and (2) when renal deposits of fibrin have been proved, fibrinuria is sometimes absent.

Fibrin or fibrinoid can be detected in second-set rejections (Dempster 1953a, Pineo et al 1971) and first-set rejections of the vascular obliterative type. Fibrinoid deposits in the glomeruli and afferent arterioles and interlobulars are constant in second-set rejections but only occasional and focal in first-set rejection. McKenzie and Whittingham (1968), for example, detected focal deposits of fibrin in only 32 percent of rejecting first-set kidneys. In late onset first-set rejections, Porter (1967) detected fibrinogen in 17 percent and this was accompanied by IgM. The detection of fibrin under the conditions reported by these investigators indicates that fibrin deposition is the end-result of a process which disturbs the vascular endothelium and intima and together with a preceding increased vascular permeability evokes an afferent vasoconstriction, leading to underperfusion of the outer cortex. If, as Antoine et al (1969) reported, fibrinuria does not occur in a proportion of such cases, it is possible that this is because glomerular filtration of the affected glomeruli has stopped. Underperfusion of the cortex would certainly lead to some degree of renal failure.

Why fibrin should be deposited in first-set transplanted kidneys undergoing acute classical rejection is not easy to understand because of past difficulty in demonstrating fibrin or fibrinoid by histochemical means. Salaman (1970) reported increased ^{125}I-fibrinogen radioactivity in transplanted kidneys during acute rejection and the biopsy illustrates that acute classical rejection was considered to be the diagnosis. After the transplantation of a cadaver kidney and immediate anuria, a biopsy is limited in allowing one to arrive confidently at a diagnosis of acute rejection as against a similar lesion found in most cases of acute renal failure. Unless a biopsy includes interlobular arteries, in which case there is usually severe bleeding, fibrinoid necrosis can be missed and the damage to the tubules of the outer cortex assumed to be due to ischemia alone (Figure 6 a, b).

Pineo et al (1970) detected protein-bound radioactivity in the urine from both normal and

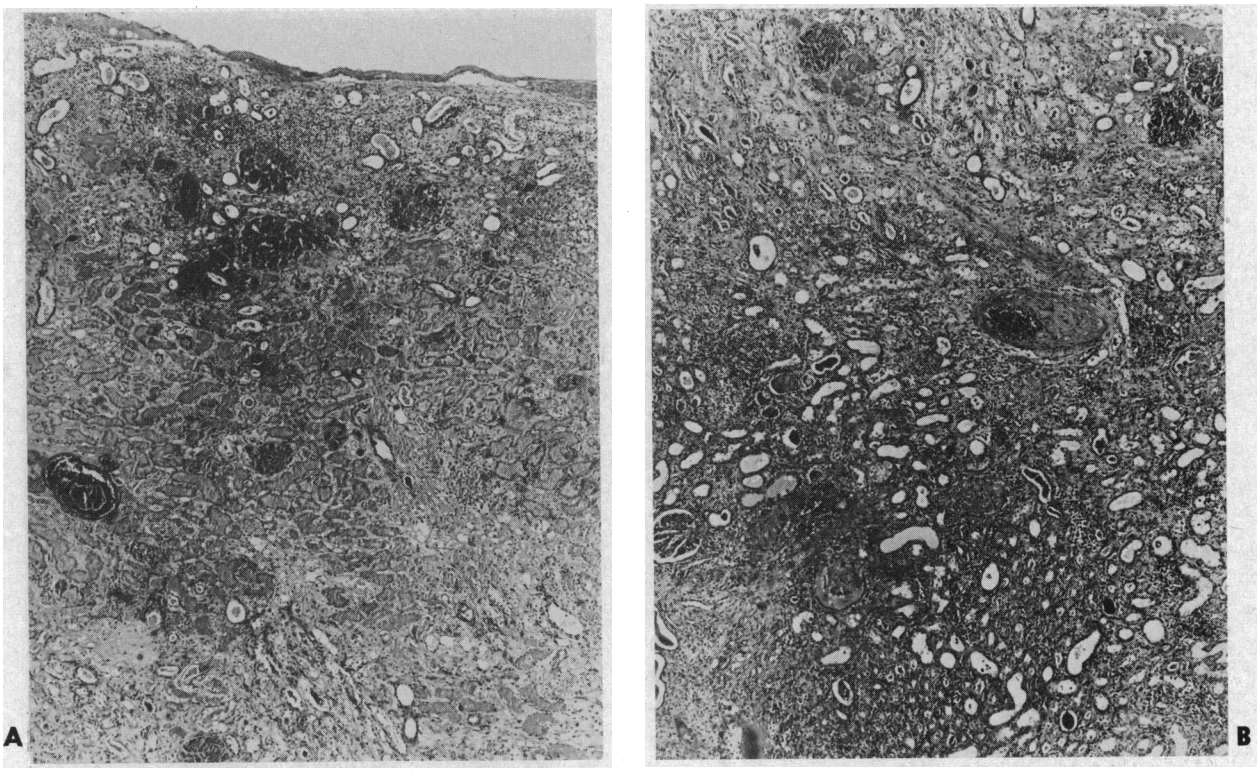

Figure 6.—(a) Section of a human cadaveric first-set transplant removed after 10 days without functioning. The outer cortex resembles the features of cold ischemia damage alone. Picro-Mallory x 80. (b) Section of the same kidney but photographed a few mms. further into the cortex. The obliterative vascular lesion of an interlobular is now clearly demonstrated. The diagnosis of immediate anuria would probably be—initially cold ischemic damage followed later by the early onset of the obliterative vascular lesion in which fibrinoid necrosis occurs in the early stages. Picro-Mallory x 80.

rejecting second-set allotransplanted kidneys in any given animal. Like the fragments detected by Antoine et al (1969), the radioactivity was bound to high molecular weight protein but the significance is not understood although the excretion of such substances denotes increased vascular permeability, known to be present early, rather than local fibrinolysis. Since plasminogen levels were the same in renal and peripheral circulations, it would indicate that local fibrinolysis is not occurring at an increased rate. The conclusion appears to be that systemic coagulation plays no role in second-set rejections and intrarenal coagulation follows severe vasomotor disturbances within the kidney which are fundamentally responsible for the onset of acute renal failure (Pineo et al 1970; Dempster 1971). Colmen et al (1969) came to a similar conclusion in rejecting the concept that hyperacute rejection was an analogue of the generalized Shwartzman reaction. It should be pointed out, however, that to claim a primary role for coagulation in the Shwartzman reaction is debatable since it is suppressed by renal denervation, reduced in severity by phenoxybenzamine and is dependent on functional defects of the reticulo-endothelial system. In a more recent assessment of immediate posttransplant anuria, Starzl et al (1970) withdrew their previous view that the second-set kidney transplant reaction was a Shwartzman reaction. Their assessment is now close to the original view expressed by Dempster (1953a).

Hyperacute Rejection—
A Second-Set Reaction or Not?

Without adequate controls involving hemodynamic upsets due to hemoconcentration or hypovolemia in autotransplanted kidneys, one is in some difficulty in assessing the immunological significance of anurias designated "hyperacute rejection." At best, hyperacute rejection is better known as second-set rejection—that is, the reaction which occurs when an animal is sufficiently sensitized by a rejected and once viable trans-

plant and a sufficiently long interval of time has been allowed to elapse before the animal is challenged again with a kidney allotransplant. It is by no means clear, in many cases, whether hyperacute rejections are second-set rejections or not. Except for the reports of Williams et al (1969) and Nakamoto et al (1967) on the fate of a proportion of second kidney transplants from different donors, a technical factor—hypovolemia or poor preservation, for example—could explain the immediate post-transplant anuria which is a less dogmatic term than "hyperacute rejection." Evidence for pre-existing HL-A antibodies may (Kissmeyer-Nielsen et al 1966) or may not (Turcotte et al 1970) be associated with irreversible anuria. The reports of hyperacute rejection incriminate previous sensitization by pregnancy antibodies or blood transfusion antibodies. This, in effect, incriminates the leukocytes as sensitizers but these cells have failed, experimentally, to sensitize recipients against kidney and heart transplants (Calne et al 1966). It is in this context that one must view with some scepticism the claims that some immediate anurias are hyperacute rejections in the sense that HLA-sensitization had occurred before the transplant.

By formal experimentation, one can arrange a series of second-set rejections so as to provide some data concerning the functional, hemodynamic, microscopical and immunological aspects of such reactions. From such experiments it can be established that the tempo and the intensity of the reaction varies and that, in a percentage of subjects which appear to have been adequately sensitized, no second-set reaction occurs at all (Pineo et al 1970). It has also been established that the earliest arteriographic evidence capable of explaining the sudden onset of oliguria or anuria involves outer cortical exclusion from perfusion (Pineo et al 1970; Dempster 1971a). Rather than a generalized vasoconstriction of the whole arterial tree, as previously suggested (Dempster 1953a), the earliest damage would appear to be in the afferent arterioles and glomeruli of the outer cortex, general afferent vasoconstriction follows later. Previous arteriographic assessments of the nature of second-set rejections were made at 12 or 24 hours after transplantation; in most cases this would be many hours after the onset of anuria (Dempster 1953a). Arteriography at this late stage demonstrated generalized vasoconstriction and the interpretation was that anti-kidney antibodies were mopped up by the vascular endothelium generally, so leading to a state of generalized vasoconstriction due to a supersaturation by anti-kidney antibodies.

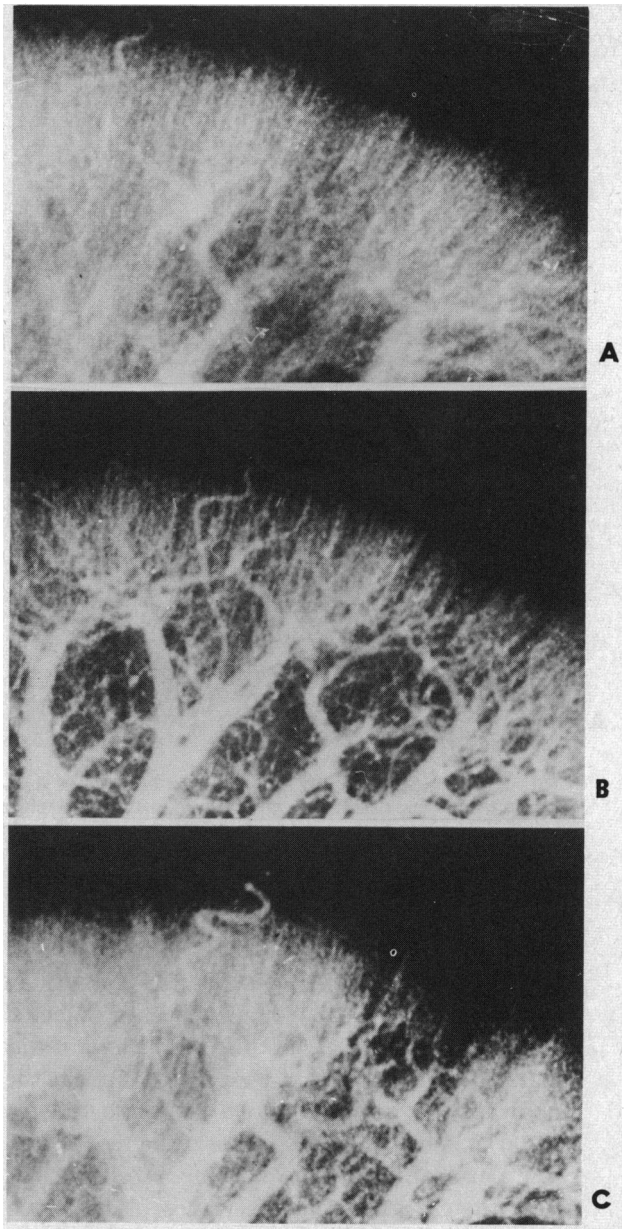

Figure 7.—Successive arteriograms over a period of six hours in a second-set kidney transplant rejection. (a) Immediate post-transplant oliguria. (b) Two hours later anuria has occurred. (c) Two hours later the anuric state continues and now the renal blood flow is reduced markedly. (Pineo G F, Regoeczi E and Dempster W J, 1970): Brit J Exp Path 51:547-562, 1970).

Recent experiments (Pineo et al 1970) have indicated that the first sign of the second-set re-

action is inadequate perfusion of the outer cortex and this is associated with severe oliguria or anuria (Figure 7). The generalized vasoconstriction which is evident in second-set kidneys left in situ for 12 to 24 hours after the onset of anuria or oliguria might reasonably be explained by increased renal peripheral vascular resistance. To this should be added vascular damage resulting in areas of fibrinoid necrosis which probably induces some degree of vasoconstriction (Dempster 1953a). It would appear, therefore, that anti-kidney antibodies are first deposited on the glomerular basement membrane and only later in the rest of the renal afferent vessels. This can be explained by the classical reasons of increased hydrostatic pressure and tenuous endothelium in the glomerular capillaries. Since previous grafting with skin can evoke antibodies against the coronary vessels and so produce a second-set heart transplant reaction (Dempster 1968), it is not to be expected that this type of antibody would be exclusively anti-glomerular basement membrane. This is supporting evidence that several tissues contain common antigens in their capillary systems (Krakrower and Greenspon 1958). One must look more closely at the glomeruli and afferent arterioles in order to understand the earliest changes since it is likely that damage occurs simultaneously in glomeruli and afferent arterioles.

Now that the significance of the HL-A cytotoxins in relation to hyperacute rejection is so equivocal and contradictory (Stewart et al 1969; Patel and Terasaki 1969), little is to be gained by taking up entrenched positions and attempting to explain exceptions to the poorly established rule as false negatives or false positives (Heale et al 1969; Morris et al 1969). Turcotte et al (1970) have described several cases of immediate post-transplant oliguria or anuria. There was poor function in 21 out of 29 cases, which is an extraordinarily high incidence and especially since the donors were live and related. Of these, two were positive HL-A cross matches but both recovered function subsequently. Poor function in the immediate post-transplant phase was attributed, by these observers, to hypovolemia and to an antibiotic, cephalothin—that is, technical factors. The evidence with respect to cephalodin as a nephrotoxic agent is equivocal and a more likely cause is the "flush out" solution. These investigators might have looked again at the flush out used – Ringer-lactate solution, which can also disturb renal hemodynamics after transplantation. The recipients were not hydrated, which also can lead to post-transplant oliguria or anuria. So little was the concern for the number of blood transfusions and pregnancies that no information is provided by the investigators, but there would appear to be more males than females involved in this high series of post-transplant oliguria. Whether kidney transplant recipients are positive or negative for HL-A antibodies is irrelevant clinically. These antibodies are irrelevant experimentally since injected lymphocytes (by subcutaneous, intraperitoneal or intravenously) do not sensitize a recipient to a kidney or a heart subsequently transplanted (Calne et al 1966; Dempster 1969a). Some correlation between antigens of leukocytes and skin were reported by Medawar (1946) but I have never been able to confirm this in dogs, and the data on humans are not convincing. The debate as to whether pregnancy or blood transfusions are responsible for these hyperacute rejections is based on evidence so tenuous and contradictory that it can hardly be taken seriously. Pregnancy and blood transfusions were in the background from the beginning of kidney transplantation, so what has happened in recent years to bring about the recent spate of reports about hyperacute rejection caused by previous sensitization?

From a period when no one seemed to be experiencing any immediate post-transplant anurias we are now in a phase when it has become, or perhaps was, a major pre-occupation of most clinical units. Partly, this is due to the fact that second kidneys are being transplanted more frequently in the last three years than previously. Early post-transplant anuria, in a proportion of these second kidneys, is undoubtedly due to pre-existing anti-kidney antibodies developed against the rejected first kidney and some degree of cross-sensitization can account for this (Williams et al 1969). Partly, the universal use of cadaveric kidneys has led to a high incidence of post-transplant anuria from which many recover normal or adequate renal function. Since Najarian et al (1966) were courageous enough to admit frankly to several cases of immediate post-transplant anuria due to inadequate hydration and most probably hypovolemia which is a known cause of renal vasoconstriction (that is, technical rather than immunological causes), a climate has been

created wherein post-transplant anuria can be discussed without loss of face. Turcotte et al (1970) have recently admitted to immediate satisfactory function in only eight out of 29 human allotransplants.

The history of immediate post-transplant anuria is similar to that of "dumping" after gastrectomy: at first, few would acknowledge the reality of this complication while later anyone not encountering this and other complications after gastrectomy could not be regarded as serious gastroenterologists. A classification consisting of four different types of post-transplant anuria (Dempster 1954, 1963) was generally regarded, even a few years ago, as rather bizarre. For instance, Hamburger et al (1964) commented, with a touch of ridicule, "It is also possible that Dempster has observed the same phenomena, but this author seems to encounter so many more anuric complications than the other groups, even in autotransplantation, that the interpretation of his findings is not easy." What Hamburger et al (1964) failed to appreciate was that Type 4 anuria was deliberately produced by the second-set reaction, requiring to be set apart from Type 3, the usual first-set rejection anuria, and Types 1 and 2, immediate post-transplant anurias occurring in autotransplants as well as in first-set allotransplants. It is Type 4 anuria due to a second-set type of rejection, which has now become an important clinical problem. Indeed, Hamburger et al (1962), without producing any objective evidence, claimed that preexisting antibodies were responsible for two of their three cases of immediate post-transplant anuria; this is equivalent to suggesting that a second-set rejection was responsible (that is, anuria in a previously sensitized animal); such a reaction is classifiable as a Type 4 anuria. In their report on immediate post-transplant anuria in live first-set kidneys a figure of 50 percent was given, a rather high figure.

Kissmeyer-Nielsen et al (1966) in their report of hyperacute rejection seemed unaware of the literature on second-set kidney rejection since they could find no parallel to their own two cases of immediate post-transplant anuria other than the "white skin graft." The second-set kidney rejection is a phenomenon which has to be measured in minutes or hours whereas the "white skin graft" can be either a technical failure or not and requires a few days to develop. Other clinical groups have also failed to establish experimentally the necessary criteria for assessing second-set kidney rejection (Williams et al 1969; Starzl et al 1968).

In the discussion of the paper by Najarian et al (1966), Hume reiterated his view that with adequate hydration one should never encounter immediate post-transplant anuria in first-set kidneys and, if one does, the cause is probably technical due to hypovolemia in humans or hemoconcentration in dogs. With this view I am essentially in agreement. The data missing from Hume and Egdahl (1955), however, is the incidence of post-transplant anuria without adequate hydration, which must surely have provided the incentive to hydrate the animals before transplantation. It is interesting that the latest figures from Hume's group (Williams et al 1969) admit that four out of five first-set transplants failed to function and that in three out of these four the failure could fairly be claimed to be due to technical causes.

In a review of the growing problems of clinical renal transplantation, Dempster and Kountz (1966) drew attention to the probable complications of transplanting a second kidney from a different donor in man; the danger being, in a significant proportion, of cross-sensitization precipitating a second-set rejection which would present as immediate post-transplant anuria. Hume et al (1966) challenged this warning rather prematurely: "The results of second kidney transplants in man to date, however, do not seem to bear out either of these contentions." Yet, three years later there was a change of emphasis: "During the past two and a half years, ten of sixteen secondary renal allografts performed at the Medical College of Virginia did not function. This experience has been disconcerting since 11 of the secondary grafts carried out prior to 1967 functioned." The above data highlight the way medical experience develops and emphasizes the limitations of publishing insufficient data too soon. Stated another way, over a period of four years, 27 second kidney transplants were performed; of these, ten failed to function, which gives a cross-sensitization figure of 37 percent. This corresponds to the predicted data in humans as derived from skin grafting (Rapaport et al 1962) and from canine kidneys (Dempster 1953a). It is probable that a range of 30 to 45 percent may be a reasonable forecast although the figures reported by Naka-

moto et al (1967) are surprisingly high. The only means, at present, of finding out whether a second transplant will be rejected immediately is to transplant and await events. Alternatively, it would be essential to lymphocyte type and attempt to correlate second-set rejection due to an overlap of lymphocyte antigenic factors. But lymphocyte typing is so unreliable that this will probably be a fruitless task. It is this series of post-transplant anurias (Type 4—Dempster 1954, 1963, 1969a) which can be regarded, until proved otherwise, as second-set rejections due to cross-sensitization or to a wide spectrum of antibodies being evoked by the rejection of the first kidney.

The real debate concerns the significance of immediate post-transplant anuria in first-set kidneys and the validity of incriminating, as sensitizing agents, antibodies evoked by pregnancy or blood transfusions or both. Patel and Terasaki (1969) reported that in 14 percent of 157 first-set transplants in females and 6.3 percent of 256 first-set transplants in males there was immediate post-transplant anuria. This would suggest that this complication is more frequent in females and since both sexes are dialysed or are blood-transfused before transplantation the discrepancy can be explained more easily by pregnancy cytotoxins. However, it is evident from the data so far that parous females are no more liable than males to immediate post-transplant anuria.

There is considerable dispute concerning the relationship between pre-existing cytotoxins due to blood transfusions or pregnancy and immediate post-transplant anuria. Terasaki et al (1967) reported that a woman had immediately rejected a kidney from her husband by whom she previously had borne two healthy children. Without any details of the cross-match test it was assumed that the cause of this immediate post-transplant anuria was pregnancy antibodies.

It should be appreciated that pregnancy leucoagglutinins are complete antibodies whereas antibodies derived from multiple blood transfusions are usually incomplete (Engelfriet and van Logham 1961). Thus, two different types of antibody and sometimes a combination of the two are supposedly involved in hyperacute rejection. If leucocytotoxins are identified then, again, they are entities different to leucoagglutinins. Furthermore, more than three pregnancies are required to raise the leucoagglutinin titre to detectable levels (van Rood et al 1959); the number of blood transfusions required is not yet agreed upon but no effect has been encountered after over a hundred.

There is no evidence that HL-A antigens cross-react with glomerular basement membrane (Dixon 1969) which is the target in second-set reactions in kidney allotransplants (Dempster 1953a) and in long surviving human first-set kidneys after reversal of early rejection episodes. Is there any evidence that HL-A antigens cross-react with vascular endothelial cells?

The conflicting views regarding pregnancy as a period of immunological inertia (Anderson 1965) or intense immunological activity (Terasaki et al 1967) are clearly not reconcilable at present. This conflict is reflected in contradictory reports and views. If a fetus evokes no more maternal reaction than the production of low titre leucocyte antibodies one need not regard pregnancy as a period of intense immunological activity, especially since several pregnancies are required to evoke a detectable titre. As with Rh sensitization, only when the maternal circulation is invaded does sensitization occur. Antigen administered intravenously is not generally regarded as effective. This attitude is derived from experiments conducted by Medawar (1946) in which leucocytes injected intravenously did not sensitize whereas they did when injected intradermally. This concept is of no practical validity since allotransplanted organs can very effectively sensitize via the intravenous route. The view of Terasaki et al (1967) quoted above is in strange contrast to that of Ceppellini et al (1966) who reported ". . . the two grafts with the longest survival were observed in a recipient woman who had ended her pregnancy three months before grafting." This implies, for some unknown reason, a connection between pregnancy and the length of survival of skin grafts. Granted that leucoagglutinins are developed during pregnancy, should this form of sensitization endure for all time when it is, theoretically, no different from sensitization by a skin graft? Rapaport and Converse (1958) reported that sensitization by a skin graft may disappear by 80 days in spite of the fact that a skin graft is widely considered to be the most potent transplantation sensitizing agent.

The conclusion drawn by Terasaki et al (1967) is rather undermined by the surprising data of Goodman and Masaites (1967) which shows

that, in a study of 1553 women, the incidence of pregnancy antibodies is less after the second pregnancy than after the first. Thus, women are at less risk after the second pregnancy—if, indeed, there is any risk at all engendered by these antibodies. Serum which reveals cytotoxicity *in vitro* may not be toxic *in vivo,* and this difference has still to be evaluated. What credence can be given to the claims that pregnancy antibodies cause immediate second-set rejection of a first-set kidney allotransplant when these same antibodies cause no damage to fetal leucocytes against half (that is, the male contribution) the antigens of which they were developed in the first place?

Ever since Erhlich discovered antibodies in the serum of pregnant women various speculations as to the diseases they may cause have ranged from toxemia of pregnancy to fetal abnormalities. Recent analyses refute any connection between pregnancy cytotoxins and fetal abnormalities or neonatal leucopenia (Berah et al 1966). These investigators even dispute the report of Jensen (1962) that the antibodies are more frequently developed in premature babies; their data support the opposite view. Halbrecht and Komlos (1968), in a rather small series, return to the theme that pregnancy abnormalities are due to HL-A incompatibility. Their testing was done with the mixed lymphocyte (husband-wife) test; with two normal pregnancies there was good matching, but at the other end of the scale hydatidiform mole was associated with an increased number in transforms. Since there would appear to be no correlation between the lymphocyte transform test and HL-A leucocytoxicity tests (Debray-Sachs 1968) one is in no position to draw any definite conclusions.

Correlations with Length of Survival

There are many facets to rejection (Table 4) so that to try to correlate lymphocyte typing alone with length of survival is unrealistic. It is seldom possible to control immuno-suppression rigidly in a whole series of cases because of clinical complications. All these aspects must be assessed before one may come to any conclusions about histocompatibility factors and length of survival.

A distinction should be drawn between lymphocyte typing which is now progressing satisfactorily and the actual histocompatibility relationship to other tissues. Just because the HL-A system is a genetic antigenic polymorphism does not automatically link it to tissue histocompatibility any more than other such polymorphisms—serum β-lipoproteins, haptoglobins, serum cholinesterase and the like. Although there appears to be common antigens to skin and heart and kidney, there is little evidence to convince one that lymphocytes can sensitize a recipient to a subsequently transplanted kidney or heart. In fact, the standard method of sensitizing is now by skin grafting (Dempster 1953c) since lymphocytes have proved useless in the larger mammals (Calne et al 1966; Simpson et al 1970). Having encountered this problem with lymphocytes, the author was provided with the incentive to seek other tissues, like skin, with antigens in common with kidney. But even when a highly successful tissue such as skin is used to presensitize, a few instances of failure to evoke a second-set reaction in allotransplanted kidneys have been reported (Pineo et al 1970; Najarian 1970). Sometimes, also, the Shwartzman reaction itself fails to occur after the second challenge of endotoxin.

Considering that virtually nothing is known about the mechanism of lymphocytotoxicity against grafts *in vivo* or the strengths of the HL-A antigens *in vivo* or whether any one is of critical importance for rejection *in vivo* and the fact that HL-A antibodies *in vivo* have not even yet been categorized with respect to (1) their degree of affinity, (2) their ability to fix complement *in vivo,* (3) their cytotoxic role if not complement-fixed *in vivo,* (4) the site of union of antigen and antibody *in vivo* and its sequelae as well as the recognized necessity of using skin rather than lymphocytes to presensitize experimentally against organ transplants—considering those points it was by an extraordinary *tour de force* of mass persuasion that claims were pushed for HL-A antigens as precise markers of exact degrees of histocompatibility with respect to transplant survival. If, even now, no convincing correlation has been found between graft survival and 25 HL-A antigens (including the commonest and the allegedly strongest) it is unlikely that a correlation will be established by discovering more rare antigens.

The characteristics of the second-set kidney transplant reaction (hyperacute rejection—when genuine) can now be set down:

TABLE 4.—*Possible Correlations in Tissue Matching*

TISSUE MATCHING

1. Varying sera
2. Increasing antigen detection
3. Varying criteria of matching and mismatching

Successive Kidneys

Pre-existing Cytotoxins } Blood transfusion / Pregnancy

First-set Kidneys

Skin Antigens

Genetic Relationship

RENAL FUNCTION

Good match – good function?

Mismatch – poor function?

TISSUE DAMAGE

Frequently more severe than the clinical state betrays.

REJECTION EPISODES IN EARLY STAGES

Severe / Moderate / Mild } Stage at which detected and treated.

Basement Membrane Antigens

REJECTION EPISODES IN LATE STAGES

SURVIVAL

Severe / Moderate } Good match

Mild } ? less rejection

STATE OF DONOR KIDNEY

1. Age of donor
2. Degree of ischemic damage: anuric 10 days < less / more
3. Pre-existing disease, *e.g.* pyelonephritis.

STEROID TOLERANCE AND DIFFERENCES IN REACTIVITY

1. Tolerance of large doses in early stage < good / poor
2. Utilization of large dose in early rejection < good / poor
3. Tolerance of maintenance doses and utilization < good / poor
4. Tolerance of prolonged high steroid dosage < good / poor
5. Presence of complications requiring reduction or withdrawal of steroid < Yes / No

• Adequate presensitization is not invariably followed by a second-set reaction (Pineo et al 1970; Najarian 1970).

• It is not dependent on complement fixation *in vivo* (Dempster and Brown 1971).

• It is not abrogated or reduced in severity by rendering incoagulable the blood of recipients (Pineo et al 1970).

• Systemic intravascular coagulation is not the primary factor (Pineo et al 1970).

• Renal vasoconstriction, especially of the outer cortical vessels, is the first sign of the reaction (Dempster 1953a; Pineo et al 1970; Dempster 1971).

• Once started, the reaction proceeds inexorably to profound irreversible parenchymal damage with fibrin deposition in the glomeruli and afferent arterioles (Dempster 1953a; Pineo et al 1970; Dempster 1971b).

• Polymorphonuclear cells are not consistently sequestered in the capillaries of the damaged glomeruli (Dempster 1953a; Pineo et al 1970; Dempster 1971). Such cells may be observed in autotransplants following a hemodynamic upset and hence cannot be the effectors of allogenic or xenogenic rejection (Dempster 1953b).

• The renal vascular basement membrane bears the brunt of the reaction (Dempster 1969 a; Pineo et al 1970). Basement membrane antigens are not represented on lymphocytes so that it is quite improbable that HL-A antibodies are involved since they are complement fixing—*in vitro*, at least. This is the most important single factor against a hypothesis that lymphocytes act as significant histocompatibility markers.

On this evidence, it is even difficult to fit the second-set kidney transplant reaction into any class of renal antigen-antibody reactions. In

acute glomerulonephritis, for example, there may be renal hyperemia and a concentrated urine may be produced—the exact antithesis of the second-set reaction. There is, on the other hand, a certain similarity (but no more than that) to the Shwartzman reaction (Dempster and Brown 1971) and to a very severe Masugi nephritis (Shigematsu 1970). The second-set kidney transplant reaction is independent of complement fixation *in vivo* whereas all the current indicator systems and reports (Kissmeyer-Nielsen et al 1966) of cross-reactivity of serum with kidney homogenates involve complement fixing antibodies—*in vitro*. Further, the actual site of union of antigen and antibody and its cytopathology were not established, which is crucial because cross-reactivity is no proof of cytotoxicity. The ultimate test of histocompatibility is not derived from an *in vitro* test, but from the actual *in vivo* behavior of the recipient. Claims (Starzl et al 1970) of second-set rejection by HL-A antibodies not even detectable in the serum cannot be discussed seriously.

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INFECTION FROM BRONCHODILATOR SPRAYS

A troublesome complication in patients with chronic respiratory insufficiency is the transmission of infection by various bronchodilator aerosol devices. . . . The most common organism sprayed into the hospitalized patient is pseudomonas. It's very difficult to eradicate; it occurs in the large bulk nebulizers, particularly the heated devices; and it requires a meticulous program of sterilization and cleansing of the equipment and daily changing. You just can't reuse any part of the machine or apparatus which has been exposed to the expired air from another patient.

Home management of the various inhalation therapy devices is somewhat easier because the patient is not exposed to the hospital organisms. But the possibility of infection still must be considered. You can't just give a patient a machine and tell him to wash it out once in a while. He's got to have a good program where he washes the unit and all the exposable parts with soap or perhaps a detergent. A useful system, if the patient has a nebulizer powered by a compressor, is to have him aerosolize 0.25 percent acetic acid or about 6 cc of white vinegar into a pint of water every couple days for about 10 minutes.

—PHILIP KIMBEL, M.D., Philadelphia
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